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EXAMINER	
STAPLES, MARK	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,799	JOHANSEN, JACK T	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/05/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 are pending and at issue.

Applicants' arguments filed on 03/05/2007 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

2. It is acknowledged that that the specification has been amended to indicate priority to the provisional application.

3. The objection to the specification under 35 U.S.C. 112, first paragraph is withdrawn in light of the Applicant's explanation of the cited language being acceptable and understandable in the art.

4. The objection to the abstract is withdrawn in light of the Applicant's amendment of the abstract.

5. The objection to the improper use of trademarks is withdrawn in light of the Applicant's amendment of the trademarks.

6. The objection to claim 8 is withdrawn in light of Applicant's remarks and upon closer inspection of the claim set on file. The extra "period" in the claim appears to be a stray mark.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

7. The rejection of claim 22 under 35 USC § 112 Second Paragraph is withdrawn. Applicant's arguments with respect to this rejection, see section 7 for the 2nd and 3rd sentences on page 7, filed 03/05/2007, have been fully considered and are persuasive.

The rejection of claim 13 under 35 USC § 112 Second Paragraph is withdrawn. Applicant's arguments with respect to this rejection, see section 7 in the 1st full paragraph on page 7, filed 03/05/2007, have been fully considered and are persuasive.

Claim Rejections Withdrawn -35 USC § 102(b) and 35 USC § 103(a)

8. Applicant's arguments, see sections 8 and 9 on pages 7-9, filed 03/05/2007, with respect to the rejections of claims 1-27 under Lu et al. (1994) as the primary reference have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, new grounds of rejection are made in view of Bambara et al. (1974) as the primary reference.

Double Patenting Rejection Withdrawn

9. Applicant's arguments, see the 6th to 10th sentences of the 2nd full paragraph on page 9, filed 03/05/2007, with respect to the provisional rejection(s) of claim(s) 1-27

under Double Patenting have been fully considered and are persuasive. Applicant persuasively argues that the claims of the instant application do not overlap in scope with the claims of pending Application No. 10/159,322. Therefore, the rejection has been withdrawn.

Rejections Maintained

Claim Rejections Maintained - 35 USC § 112 Second Paragraph

10. The rejections of claims 4, 5, and 27 under 35 USC § 112 Second Paragraph in recitation of the terms "substantially free of" and "substantially increases" being undefined relative terms are maintained. In this particular application these terms are not defined and the metes and bounds cannot be determined by this language. At the top of page 7 of the response, Applicant argues that impurities of salts may be present. However, "substantially free of" is not limited to impurities alone but includes the preparation of solutions with a metal salt as a component; the language does not put any definable bound on how much metal salt may be in the solution and still be within the claimed invention. Likewise, one might add salt to increase the salt concentration over time, but there is no definable bound on how much one might add and be within the claimed invention. Therefore, these rejections are maintained.

11. The rejection of claims 1-27 under 35 USC § 112 Second Paragraph as omitting essential steps is maintained. As claim 1 is now written, a reasonable interpretation would be that the solution increases in pH spontaneously over time. Applicant argues

against this being the intended claimed invention by specifically arguing for active steps (see 2nd full paragraph on p. 7 of response filed on 03/05/2007). Applicant argues that the pH of the solution is adjusted by active, but omitted, steps; for example by: "adding base to the solution" or "increasing the ratio of higher pH buffer to lower pH buffer". Thus claim 1 needs to recite some active step which conforms with the intended claimed invention. And while minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986). One suggestion would be to rewrite the claim to set forth the defined methods, as by reciting in claim 1: "c) eluting said target oligonucleotide by increasing the pH of said solution over time, wherein . . . ".

New Rejections

35 USC § 102(b)

12. Claims 1-8, 10, 12, 14, 16, 18, 19, 24, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Bambara et al. (1975), cited on the Information Disclosure Statement, IDS.

Regarding claims 1, 2, 6, and 12, Bambara et al. teach a method of separating a target oligonucleotide, a primer, from an impurity, urea, in a mixture comprising said target oligonucleotide and said impurity of, using a titratable anion exchange composition, comprising the steps:

a) binding the primer target oligonucleotide to the titratable anion exchange composition of DEAE-cellulose, DEAE being a titratable tertiary amine and cellulose being the support to which the DEAE is conjugate;

b) passing a solution through said titratable anion exchange composition with target oligonucleotide bound thereon, wherein said solution increases in pH from 7.5 to 8.5 over time; and

c) eluting said target oligonucleotide, wherein said impurity elutes at a different pH than said target oligonucleotide (entire article, especially the first full paragraph in 2nd column on p. 4608).

It is noted DEAE-cellulose is N,N-diethylaminoethyl ether cellulose (CAS No. 9013-34-7).

Regarding claims 1-3, 6, and 12, Bambara et al. teach a method of separating a target oligonucleotide, a primer, from an impurity, "failed primers" using polyethyleneimine-cellulose by binding in a neutral solvent containing 1.2 M LiCl – 7 M urea solvent followed by pH increase to 8.5 (entire article, especially the first full paragraph in 2nd column on p. 4608 and Figure 9).

Regarding claims 4 and 5, Bambara et al. teach use of 0.2 M triethylamine bicarbonate buffer at pH 7.5 which is substantially free of metal salts followed by 0.2 M triethylamine bicarbonate buffer at pH 8.5 which has no increase in salt concentration.

Regarding claims 7 and 8, Bambara et al. teach a synthetic polyacrylic polymer of acrylamide and bisacrylamide which contains secondary amines (see last paragraph in 1st column on p. 4608).

Regarding claim 10, Bambara et al. teach a method wherein said target oligonucleotide is a synthetic oligonucleotide, a primer (see the first full paragraph on p. 4608).

Regarding claim 14, Bambara et al. teach a method wherein a solution increases from a pH of 7.5 which is about 8 to a pH of 8.5, which is about 11 (entire article, especially the first full paragraph in 2nd column on p. 4608).

Regarding claim 16, Bambara et al. teach a method wherein said target oligonucleotide has a length of 12 which between about 8 to about 11 nucleotides (see paragraph 8 in 1st column on p. 4608).

Regarding claim 18, Bambara et al. teach a method wherein said impurity is one or more failure sequences, "failed primers" (see Figure 9).

Regarding claim 19, Bambara et al. teach a method wherein said impurity is the metal salt LiCl (see the 1st sentence of the first full paragraph in 2nd column on p. 4608).

Regarding claim 24, Bambara et al. inherently teach a method a method that concentrates the starting sample by teaching loading that starting sample onto a DEAE-cellulose in which the target primer becomes bound, that is, concentrated (see the 3rd sentence of the first full paragraph in 2nd column on p. 4608).

Regarding claim 25, Bambara et al. teach a method with a washing step prior to eluting the primer (see the 3rd sentence of the first full paragraph in 2nd column on p. 4608).

Claim Rejections - 35 USC § 103(a)

13. Claims 13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claims 1 and 6 above, and further in view of Lu et al. (1994), cited on the IDS.

Bambara at al. teach as noted above

Regarding claims 13 and 17, Bambara et al. do not specifically teach increasing pH in leaner manner or elution of oligonucleotides at different pH's.

Regarding claim 13, Lu et al. teach a method where a solution increases in pH in a linear manner over time (See Figure 1 for linear increases at 1 to 10 minutes and 33 to 37 minutes).

Regarding claim 17, Lu et al. teach a method wherein said impurity is one or more oligonucleotides having a shorter length, peak 1 = d(AA), than said target oligonucleotide, peak 3 = d(AAT) , and wherein said impurity elutes at a lower pH of about 10.4 than said target oligonucleotide elution pH of about 10.6.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Bambara et al. by a linear gradient with elution of different oligonucleotides at different pH's as suggested by Lu at al. with a reasonable expectation of success. The motivation to do so is provided by Lu at al. who teach that linear gradients can separate different oligonucleotides by elution at different pH's. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Lu et al. also teach the following claimed limitations which are taught in the primary reference of Bambara et al., as noted above.

Also regarding claim 5, Lu et al. teach a method with use of a pH gradient where salt concentration does not vary over time, that is, wherein the addition of solution B to solution A does not increase salt concentration over time (see p. 340, 2nd column, 2nd paragraph, 2nd sentence for the elution in pH gradient).

Also regarding claim 7, Lu et al. teach a method wherein said titratable anion exchange composition is conjugated to a support which is a synthetic polyether resin (see section 2.1 Chemicals on p. 340 for the MONO Q HR column consisting of a quaternary amine resin and see supporting document of Kralj et al. (2003) p. 2, sentences 11 and 12 for polyether resin).

Also regarding claim 10, Lu et al. teach a method wherein said target oligonucleotide is a synthetic oligonucleotide (see p. 340 section 2.1 Chemicals where mono and di-nucleotides were obtained from Sigma).

Also regarding claim 12, Lu et al. teach a method wherein binding of said target oligonucleotide with said titratable anion exchange composition occurs at a pH between 5 and 8 (see Table 1 where peak 7 elutes at pH 8 and column pH gradient[d]).

Also regarding claim 14, Lu et al. teach a method wherein a solution increases from a pH of about 8 to a pH of about 8.5, which is a pH of about 11 (See Figure 1 from 33 to 37 minutes).

Also regarding claim 16, Lu et al. teach a method wherein said target oligonucleotide has a length of 4 which is about 8 nucleotides (See Table 1).

Also regarding claim 18, Lu et al. et al. teach a method wherein said impurity is one or more failure sequences (entire reference, especially Title Figure 1).

Also regarding claim 25, Lu et al. teach a method with a washing step prior to eluting said target oligonucleotide, that is, pumping of a solvent to for about 20 minutes to restore the pH (see p. 340, 2nd column, 2nd paragraph, 6th sentence).

14. Claims 4, 8, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claims 1 and 7 above, and further in view of Asteriadis et al. (1976), cited on the IDS.

Bambara et al. teach as noted above.

Bambara et al. do not specifically teach a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH.

Regarding claim 4, Asteriadis et al. teach a method wherein a solution is relatively of relatively low salt concentration, that is substantially free of metal salts and other salts (entire reference, especially p. 65, 2nd paragraph, 2nd sentence).

Regarding claim 8, Asteriadis et al. teach a method wherein said synthetic polymer is styrene-divinyl benzene copolymer (see page 65, section Materials for AG 1-X2 and AG 1-X4 and supporting document by BIO RAD p. 2, 1st sentence identying the syntehic polymer as styrene-divinyl benzene copolymer).

Regarding claim 15, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Bambara et al. by using a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH as suggested by Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Asteriadis et al. who teach the usefulness of a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH for purification of oligonucleotides and the teaching of Bambara et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

15. Claims 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claims 1 and 10 above, and further in view of Jin-Yan et al. (WO9527718 published in 1995), cited on the IDS.

Bambara et al. teach as noted above.

Bambara et al. do not specifically teach a tertiary amine, synthetic support polymer, or a synthetic oligonucleotide which is a phosphorothioate.

Regarding claim 8, Jin-Yan et al. teach a method wherein said support is a synthetic polymer, the polyacrylic linked polymethacrylate resin which is the support for FRACTOGEL® EMD DMAE from Merck (see Merck datasheet for FRACTOGEL® EMD DMAE).

Regarding claim 11, Jin-Yan et al. teach a method using a synthetic oligonucleotide which is a phosphorothioate (entire reference, especially Title and Abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Bambara et al. by using a tertiary amine, a synthetic polymer, and a phosphorothioate as suggested by Jin-Yan et al. with a reasonable expectation of success. The motivation to do so is provided by Jin-Yan et al. who teach the usefulness of a tertiary amine and a synthetic polymer for purifying oligonucleotides which are phosphorothioates and the teaching of Bambara at al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Jin-Yan et al. also teach the following claimed limitation which is taught in the primary reference of Bambara et al., as noted above.

Regarding claim 2, Jin-Yan et al. teach a method wherein said titratable anion exchange composition comprises a tertiary amine, dimethylaminoethyl or DMAE (see p. 10, line 5).

16. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claims 1 and 8 above, and further in view of Crane et al. (US Patent 5,092,992 issued 1992).

Bambara et al. teach as noted above.

Bambara et al. do not specifically teach polyethyleneimine-derivatized silica gel.

Regarding claim 9, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Bambara et al. by using polyethyleneimine-derivatized silica gel as suggested by Crane et al. with a reasonable expectation of success. The motivation to do so is provided by Crane et al. who teach the usefulness of and polyethyleneimine-derivatized silica gel in chromatography and the teaching of Bambara et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

17. Claims 20-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claims 1 above and further in view of Fruchtel et al. (1996).

Bambara et al. teach as noted above.

Bambara et al. do not specifically teach a method wherein a target oligonucleotide is 5'-O-protected, is 5'-O-trityl protected, where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid.

Regarding claims 20 and 21, Fruchtel et al. where the target oligonucleotide is 5'-O-trityl protected (entire reference, especially p. 20 1st paragraph).

Regarding claims 22 and 23, Fruchtel et al. teach that acid condition cleave 5'-O-trityl protecting group including acetic acid (see 2nd sentence on page 20: " . . . the trityl anchoring bond can be cleaved by very weak acids such as acetic acid").

Regarding claim 26, Fruchtel et al. teach where the target oligonucleotide is is 5'-O-dimethoxy-trityl protected (entire reference, especially Scheme 41 on p 39 and footnote on page 17).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Bambara et al. by using a target oligonucleotide which is 5'-O-protected, which is 5'-O-trityl protected, where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; as suggested by Fruchtel et al. with a reasonable expectation of success. The motivation to do so is provided by Fruchtel et al. who teach the usefulness of a target oligonucleotide which is 5'-O-protected, which is 5'-O-trityl protected, where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; and the teaching of Bambara et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

18. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bambara et al. (1975) as applied to claim 1 above and further in view of Crane et al. (1992) and Asteriadis et al. (1976).

Bambara et al. teach as noted above, and it is re-noted regarding claim 27 in part that Bambara et al. teach a method wherein a solution increases from a pH of 7.5 which is about 8 to a pH of 8.5, which is about 11; teach solutions substantially free of metal salts where the change in buffer does not substantially increase salt concentration over time; teach an polyethyleneimine conjugated to solid support; and teach an amine carbonate.

Bambara et al. do not specifically teach a method wherein a titratable anion exchange composition comprises polyethyleneimine, polyimizadole, polyhistidine or polylysine conjugated to a synthetic polymer support; and the solutions comprises one or more specifically of NH_4HCO_3 and/or NH_4OH.

Regarding claim 27 in part, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Regarding claim 27 in part, Asteriadis et al. teach a method wherein a solution is relatively of relatively low salt concentration, that is substantially free of metal salts and other salts (entire reference, especially p. 65, 2nd paragraph, 2nd sentence).

Regarding claim 27 in part, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teaching of Bambara et al. by using

a polyethyleneimine-derivatized silica gel, a solution is relatively of relatively low salt concentration, and a solution of NH_4OH as suggested by Crane et al. and Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Crane et al. and Asteriadis et al. who teach the usefulness of a polyethyleneimine-derivatized silica gel, a solution is relatively of relatively low salt concentration, and a solution of NH_4OH and the teaching of Bambara et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

19. No claim is free of the prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples MS
Examiner
Art Unit 1637
May 30, 2007

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
5/30/07